PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 235-204-WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/50860	International filing date *(day/month/year)* 21.11.2003	Priority date *(day/month/year)* 28.11.2002
International Patent Classification (IPC) or both national classification and IPC G01N33/74		
Applicant NEUROSEARCH A/S et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.06.2004	02.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer van der Kooij, M Telephone No. +31 70 340-4606

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/50860

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-6	as originally filed

Claims, Numbers

11	as originally filed
1-10	received on 21.12.2004 with letter of 21.12.2004

Drawings, Sheets

1/2-2/2	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 7-10 (all partially)

   because:

   ☒ the said international application, or the said claims Nos. 9-10 (partially) (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 7-8 (partially) are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☒ the claims, or said claims Nos. 7-8 (partially) are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-6
	No:	Claims	7-10
Inventive step (IS)	Yes:	Claims	4,5
	No:	Claims	1-3 and 6-10
Industrial applicability (IA)	Yes:	Claims	1-8 (see further seperate sheet)
	No:	Claims	-

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III-1). Articles 5 and 6 PCT.

This application does not meet the requirements of Article 5 and 6 PCT, because claims 6-8 are not clear, and/or sufficiently supported and the invention is not sufficiently disclosed by the description.

III-1.1). Present claim 6 relates to a drug development method which is in fact the method of screening as defined by claim 1-5. The expression "drug development method" is not a technical feature. It follows that claim 6 has the same scope of protection and is regarded as superfluous and thereby lacking conciseness (Article 6 PCT).

III-1.2). Claims 7 and 8 encompass the use of a genus of compounds defined only by their function wherein the relationship between the structural features of the members of the genus and said function have not been defined.

In the present case the functional feature used to define the solution to the technical problem is the problem itself. The present definition of claims 7 and 8 would cover all future solutions to the problem. This means that

(1). the scope of the claimed use would not be unduly limited by including technical features of the compounds, since it is clearly not an undue limitation of the claim to eliminate what has not yet been invented, and

(2). a skilled person cannot reduce to practice a definition of the claimed subject-matter because the compounds employed in the use have potentially limitless structural possibilities, and so there is absolutely no limit to the structural variation in the compounds, including which have yet to be made.

Furthermore, the examiner can never with any certainty, ascertain whether or not such claims are ever distinguished over the state of the art, since this would entail testing all known organic compounds for its effect on the activity of the HPA axis and $GABA_a$ receptor modulating activity. Consequently this failure to identify the scope of claims 7 and 8 is a further reason for a lack of clarity (Article 6 PCT).

In addition, since the public cannot ascertain whether or not a particular compound falls within the scope of such a claim it is unclear according to Article 6 PCT.

III-1.3). According to Article 5 PCT, the claim must contain sufficient technical disclosure of the solution to the problem. In the present case however, it would be an undue burden to randomly screen undefined compounds for their activity on the HPA axis, without any effective pointer to their identity and to test every conceivable future compound for these activities to see if it falls within the scope of the claim.
Effectively, the present application is attempting to patent what has not yet been invented and the fact that a skilled person can test for the effect used to define the compounds does not necessarily confer sufficiency on claims 7 and 8.
III-1.4). The present application does not enable the skilled person to carry out the invention over the whole of the claimed area. The definition of the invention in the claim should be construed in technical terms. The definition of the compounds in claims 7 and 8 by having an activity on the HPA axis is simply a definition of the problem, containing no technical pointers to the solution. Even if in the present application the definition of these compounds would have been defined in terms of a $GABA_A$ receptor modulating activity, the skilled artisan would not know how to make and use compounds that lack structural definition because of the absence of relationship between the structural features of the members of the genus and said function.
For these reasons mentioned under points ***III-1.2).*** till ***III-1.4).***, the subject-matter of claims 7 and 8 lacks support and the scope of said claim is not sufficiently disclosed by the description as required by Articles 5 and 6 PCT.

III-2). Rule 67.1(iv) PCT and Article 34(4)(a)(I) PCT).
III-2.1). Claims 9 and 10 relate to a method of treatment practised on the human/animal body representing subject-matter which is considered to be covered by the provisions of Rule 67.1(iv) PCT by this Authority. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V-1). Rule 66.1(e) PCT.

The Applicant's attention is drawn to the fact that the present opinion expressed as to novelty, inventive step and industrial applicability refers only to matter for which an international search report has been drawn up, i.e. for a method for screening a potential candidate for using as a sedative or anxiolytica in a *non-human animal* by measuring its effect on the activity of the HPA axis and the use of the compounds zoldipem and L-838,417 (see example 1 on page 5-6) identified by said method for inducing anaesthesia, pre-anaesthesia, muscle relaxation, or sedation or for treating, preventing or alleviating fever cramps or status epilepticus (claim 8) or for treating, preventing or alleviating anxiety (claim 9).

V-2). Prior art documents.

The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: WO-A-0105222
D2: WO-A-0240700
D3: Crestani, F., et. al., *British Journal of Pharmacology*, **2000**, Vol. 131, pages 1251-1253.
D4: McKernan, R.M., et. al., *Nature Neuroscience*, **2000**, Vol. 3(6), pages 587-592.
D5: WO-A-0044752
D6: M.L. Barbaccia, et. al., *Experimental Gerontology*, **1998**, Vol. 33(7/8), pages 697-712.

V-3). Article 33(2) PCT.

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 7-10 is not new in the sense of Article 33(2) PCT.

V-3.1). In as far as claim 7 and 8 would be restricted to compounds having defined structural characteristics (see ***V-1).***), i.e. zolpidem or L-838,419 the subject-matter of these claims would not be new for the following reasons: **D3** describes zolpidem as a hypnotic/sedative agent with anti-convulsive activity which appears to be mediated via the α1-$GABA_a$ receptors (**D3**: abstract, page 1253, column 2, paragraph 2 and 3). Thus, **D3** is relevant for the subject-matter of claims 7 and 10, the latter if properly redrafted (see point ***2).***).

V-3.2). **D4** describes the anxiolytic properties of L-838,417 which are not mediated via the α1 subunit of $GABA_A$ receptors as evident from experiments with genetically modified mice having a diazepam-insensitive α1 subtype $GABA_A$ receptor (page 589, column 2, paragraph 2-page 590, column 2, paragraph 1). **D4** is therefore, relevant for the subject-matter of claims 8 and 9, the latter if properly redrafted (see above).
V-3.3). Furthermore, **D5** discloses the use of L-838,417 for the treatment and/or prevention of anxiety or convulsions, e.g. in a patient suffering from epilepsy or a related disorder (page 8, lines 6-14; claims 1, 3, 4, 9, 13 and 15). Thus, **D5** is relevant for the subject-matter of claims 7-8 and 9-10, the latter if properly redrafted.

V-4). Article 33(3) PCT.
Present claims 1-3 and 6 (as far as depending on claims 1-3) do not meet the requirements of Article 33(1) PCT, because the subject-matter of these claims is not conform the criteria of the involvement of an inventive step as set forth by Article 33(3) PCT.
V-4.1). **D1** is regarded as being the closest prior art to the subject-matter of claims 1-3 and 6 (as far as depending on claims 1-3) and discloses a method for screening for compounds having an effect on the response of the hypothalamic-pituitary-adrenal axis (HPA) to stress, comprising the steps of (a). administering said compound to a transgenic mouse with a disruption in at least one allele of the corticotropin releasing factor receptor 2 (CRFR2), (b). putting the said mouse in a stress-inducing situation, (c). monitoring plasma levels of corticosterone and ACTH in the mouse, and (d) comparing said levels to those in said transgenic mouse not placed in stress-inducing conditions. (claim 12 and 13). Compounds having a sedative effect in this model will induce less stress response in terms of increased corticosterone or ACTH release which are components of the HPA axis activity.
The subject-matter of claims 1-3 and 6 (as far as depending on claims 1-3) differs in that the compounds have to be modulators of the $GABA_A$ receptor.
The problem to be solved by the present invention may therefore be regarded as the provision of an alternative method of screening for potential sedative or anxiolytic compounds having an effect on the HPA axis.
The solution proposed in claims 1-3 and 6 (as far as depending on claims 1-3) of the present application is to use $GABA_A$ receptor modulators.
This additional requirement in the screening assay is not considered to involve an

inventive step (Article 33(3) PCT) because from **D6** it is clear that modulators of $GABA_A$ receptors affects the HPA-axis and the behavioural correlates of acute stress (abstract; page 698, first paragraph; page 710, paragraph 2). Contrary to inhibitors, activators prevent the activation of the HPA-axis, i.e reduce the plasma and brain neurosteroid, and induce less stress response. Modulators of $GABA_A$ receptors are generally know as anxiolytics and hypnotics (**D6**: abstract). Without the existence of a surprising effect assigned to the use of $GABA_A$ receptor modulators in the screening assay according to present claims 1-3, it appears that $GABA_A$ receptor modulators possess corresponding effects on the HPA-axis. It would therefore be obvious to the person skilled in the art, to apply these features of **D6** with corresponding effect to the known screening method of **D1** to come to the solution proposed by present claim 1-3 and 6 (as far as depending on claims 1-3).
Therefore, the subject-matter of claims 1-3 and 6 (as far as depending on claims 1-3) does not involve an inventive step and consequently is not conform the criteria of Article 33(3) PCT.
V-4.2). Present claims 4 and 5 appear to meet the requirements of the PCT with respect to novelty and inventive step.
V-4.3). It should be mentioned that D2 discloses similar teachings in comparison to D1 and can consequently be regarded as closest prior art as well.

V-5). Article 33(4) PCT.
V-5.1). Claims relating to methods for identifying a potential therapeutic agent according to claims 1-6 and the use of a compound for the manufacture of a medicament for the treatment of a disease according to claims 7 and 8 are generally considered as industrial applicable since they can be made or used in the biomedical industry.
Therefore, claims 1-8 are considered to fulfill the requirements of Article 33(4) PCT.
V-5.2). For the assessment of the present claims 9 and 10 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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CLAIMS:

1. A method for screening a a $GABA_A$ receptor modulator for its potential as a sedative or anxiolytica, which method comprises the following steps:
   a) exposing the compound to a test animal by administration; and
   b) measuring the effect of the compound on the activity of the HPA axis.

2. The method according to claim 1, wherein the test animal is a mouse or a rat.

3. The method according to claim 2, wherein the measurement of the activity of the HPA axis is performed by measuring, in a blood sample from the test animal after administration, the level of plasma corticosterone and/or ACTH.

4. The method according to any one of claims 1-3, comprising the further step:
   c1) selecting the compound as a sedative drug candidate if the compound substantially stimulates the HPA axis.

5. The method according to any one of claims 1-3, comprising the further step:
   c2) selecting the compound as an anxiolytica drug candidate if the compound has substantially no effect on the HPA axis.

6. A drug development method, which comprises the identification of a compound by the method according to any one of the claims 1-5.

7. The use of a compound identified as a sedative drug candidate by the method according to any one of the claims 1-4 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inducing anaesthesia, pre-anaesthesia, muscle relaxation, or sedation, or for treatment, prevention or alleviation of fever cramps or status epilepticus in a subject.

8. The use of a compound identified as an anxiolytic drug candidate by the method according to any one of the claims 1-3 and 5 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment, prevention or alleviation of anxiety.

9. A method for the treatment, prevention, or alleviation of anxiety comprising administering to said subject a therapeutically effective amount of a compound

identified as a antiolytica by the method according to any one of the claims 1-3 and 5 or a pharmaceutically acceptable salt thereof.

10. A method for inducing anaesthesia, pre-anaesthesia, muscle relaxation, or sedation, or for treatment, prevention or alleviation of fever cramps or status epilepticus anxiety comprising administering to said subject a therapeutically effective amount of a compound identified as a sedative by the method according to any one of the claims 1-4 or a pharmaceutically acceptable salt thereof.